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MEETING ABSTRACT Open Access

BEZ235 impairs gastric cancer growth by inhibition of PI3K/mTOR *in vitro* and *in vivo*

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Background

Gastric cancer at advanced stage of disease is a major health problem and the prognosis with the current therapeutic treatment strategies remains poor. PI3K/mTOR pathway mutations, especially PTEN, PI3K3C and AKT mutations and pS6 overexpression, are found frequently in gastric cancer patients and are linked with poor outcome. Thus, we evaluated the dual PI3K and mTOR inhibitor BEZ235 against gastric cancer *in vitro* and *in vivo*.

Materials and methods

Three gastric cancer cell lines (N87, MKN28 and MKN45) were treated with BEZ235 (20–80 nM) and assessed for cell viability, cell death and cell cycle distribution. PI3K/mTOR protein target modulation was measured by Western blotting. For *in vivo* studies athymic nude mice were inoculated with N87 or MKN45 cells bilaterally and treated daily with 20 or 40 mg/kg BEZ235. Tumor [^{18}F]fluorothymidine (FLT) uptake was measured via small animal PET.

Results

In vitro, treatment of gastric cancer cells with 20–80 nM BEZ235 decreased cell growth in a dose-dependent manner in all cell lines tested (up to −70%). This antiproliferative activity was linked with a G_1 cell cycle arrest (up to 75%). No significant induction of apoptosis by BEZ235 was observed. On the molecular level, BEZ235 led to a decrease of phosphorylation of AKT and S6 protein. *In vivo*, treatment with 20 and 40 mg/kg BEZ235 resulted in a significant anti-tumor effect in a N87 gastric cancer xenograft mouse model. BEZ235 therapy had no anti-tumort effect on MKN45 xenografts despite similar potent PI3K/mTOR target inhibition by BEZ235 in both xenograft models. However, expression of the proliferation marker thymidinthymidine kinase 1 correlated with sensitivity to BEZ235 *in vivo*. In line, [^{18}F]FLT uptake was significantly reduced only in the BEZ235-sensitive tumor xenograft model as measured by small animal PET.

Conclusions

In conclusion, our study shows that dual PI3K/mTOR inhibition by BEZ235 is a valuable target for gastric cancer therapy but is tumor model-dependent. Correlative studies with implementation of non-invasive imaging tools such as [^{18}F]FLT PET might be a novel and promising strategy for optimizing clinical testing of dual PI3K/mTOR inhibitors.

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